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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary	Application No.	Applicant(s)	
	09/771,302	WHITEHOUSE, MARTHA J.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of Application, Amendments and/or Claims

The amendment filed 08 September 2003 has been entered in full. Claims 35-52 are under examination.

Withdrawn Objections And/Or Rejections

The rejection of claims 35, 36, 43 and 44 under 35 U.S.C. 103(a) as being unpatentable over Laham *et al.,* J. Am. Coll. Cardiol., March 1998 (IDS submitted by Applicant, #51) in view of Deisher *et al.,* US Patent No. 5,989,866 is *withdrawn* in view of the amendment (08 September 2003).

The rejection of claims 37 and 45 are under 35 U.S.C. 103(a) as being unpatentable over Laham *et al.,* J. Am. Coll. Cardiol., and Deisher *et al.,* US Patent No. 5,989,866 in further in view of Fiddes *et al.,* US Patent No. 5,604,293 is *withdrawn* in view of the amendment (08 September 2003).

The rejection of claims 38-41, 42, 47-49 under 35 U.S.C. 103(a) as being unpatentable over Laham *et al.,* J. Am. Coll. Cardiol., in view of Deisher *et al.,* US Patent No. 5,989,866, Fiddes *et al.,* US Patent No. 5,604,293, Wilson *et al.,* US Patent No. 5,612,211 and Unger *et al.,* US Patent No. 5,244,460 is *withdrawn* in view of the amendment (08 September 2003).

The rejection of claims 35-52 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-58 of U.S. Patent No. 6,440,934 B1 is *withdrawn* in view of Applicants' convincing argument (08 September 2003).

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to a method for treating a human patient for congestive heart failure, comprising administering a single unit dose of a therapeutically effective amount of a recombinant FGF-2 (or a single unit dose of a recombinant FGF-2) or an angiogenically active fragment or an angiogenically active mutein thereof into one or more coronary vessels or into a peripheral vein in a human patient in need of treatment for said congestive heart failure, said therapeutically effective amount being about 0.2 ug/kg to 48 ug/kg of patient weight (or said unit dose comprising from about .008 mg to 7.2 mg of said recombinant FGF-2), wherein said angiogenically active mutein has at least 75% sequence identity to the FGF-2 of SEQ ID NO:2 and retains at least 50% of the angiogenic activity of FGF-2 of SEQ ID NO:2, and wherein said angiogenically active fragment has about 80% of the 146 residues of FGF-2 of SEQ ID NO:2 and retains at least 50% of the angiogenic activity of the FGF-2 of SEQ ID NO:2, wherein administration of said single unit dose provides for angiogenesis in said patient.

The instant specification teaches the administration of a single unit dose of recombinant FGF-2 in patients diagnosed with coronary artery disease (CAD). The patients were assessed using three sets of criteria; changes in exercise tolerance time, the Seattle Angina Questionnaire, and measurements of changes in the heart as assessed by MRI (page 29, line 15-page 30, line 2). The specification states that providing CAD patients with a single IC or IV infusion of rFGF-2 in accordance with the present invention provide the patients with a statistically significant physical improvement as objectively measure by MRI and other conventional criteria (page 38, lines 6-10). The specification states that in a subset of patients with congestive heart failure, improvement was seen with any dose of any dose of FGF (page 66, lines 20-23).

The subject matter sought to be patented as defined by the claims is not supported by an enabling disclosure because the specification does not teach how to make and use fragments or variants of FGF-2 that are angiogenically active and provides no assay to evaluate the function of any modified polypeptide. Absent any means to assess the function of the polypeptide, it would require an indeterminate quantity of fundamentally unpredictable investigational experimentation of the skilled artisan to determine whether any modified polypeptide could be used in the same manner as the native exemplar. Such experimentation would be undue for one skilled in this art.

Furthermore, even if an assay were provided, the specification would not support claims to FGF-2 fragments or variants modified to an unlimited extent relative to those

exemplified. In order to make a sequence variant, for example, with the reasonable assurance that it would have the desirable properties of the invention, the artisan would need to know which regions of the disclosed polypeptide are responsible for the interactions underlying its biological function(s). As is well recognized in the art, any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. It is known for nucleic acids as well as proteins, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. The disclosure provides no guidance as to which regions of the protein would be tolerant of modification and which would not, and it provides no working example of any variant sequence which would be within the claims. It is in no way predictable that randomly selected mutations, deletions, *etc.* in the disclosed sequence would afford a protein having activity comparable to the one disclosed (angiogenesis). Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517). Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as

by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

The subject matter sought to be patented as defined by the claims is not supported by an enabling disclosure because the specification fails to teach coronary angiogenesis upon administration of FGF-2, FGF-2 fragments or FGF-2 variants. Treating congestive heart failure by promoting angiogenesis is a limitation of the instant claims. None of the examples in the instant specification measure coronary angiogenic activity upon a single administration of FGF-2 fragments or variants thereof in congestive heart failure patients. Existence of working examples need not contain an example of the invention if disclosed in a manner where one skilled in the art could practice without undue experimentation but is considered a factor involving unpredictability. One skilled in the art cannot readily anticipate the effects of intravenously administering a single unit dose of FGF-2, FGF-2 variants and fragments thereof to treat coronary angiogenesis. Assays such as angiographic imaging were not employed to demonstrate neoangiogenesis. The specification fails to provide direction/guidance regarding evaluation of coronary neoangiogenesis upon administration of FGF-2, FGF-2 variants and fragments in congestive heart failure patients. The instant methods are of a complex nature. Furthermore, the instant claims encompass administering FGF-2 sequence variants, but the specification fails to teach exact structural limitations. Thus a vast number of derivatives would need to made and then screened for coronary angiogenesis. Without sufficient guidance, the changes that can be made in the structure and still maintain sufficient activity is unpredictable and the

experimentation left to those skilled in the art is unnecessarily and improperly undue. The Wells reference was submitted by the Examiner to demonstrate the unpredictability of the art regarding variants. If one skilled in the art can readily anticipate the effect, than there is predictability in the art. If little is known in the prior art about the nature of the invention, then the art becomes unpredictable.

Lastly, the subject matter sought to be patented as defined by the claims is not supported by an enabling disclosure because the specification fails to demonstrate that FGF-2 or FGF-2 angiogenically active fragments or variants thereof provide coronary angiogenesis in the patient, thus treating congestive heart failure. Applicants have provided a reference which teaches the definition and causes of congestive heart failure (Appendix A, American Heart Association). Congestive heart failure is a condition in which the heart cannot pump enough blood to the body's other organs. It occurs because the heart muscle is damaged or overworked. Causes include coronary artery disease (CAD), myocardial infarction, high blood pressure, endocarditis, and myocarditis among others. The specification is not enabling for treating the broad term congestive heart failure because congestive heart failure results from many conditions. The instant specification does not teach that administration of FGF-2, angiogenically fragments or variants thereof could treat congestive heart failure resulting from a heart valve disease, coronary artery disease and/or high blood pressure. Furthermore, the specification does not teach a nexus between angiogenic activity and treatment of congestive heart failure resulting from any of the diverse conditions as taught by the reference.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for coronary angiogenesis in the patient thus treating congestive heart failure, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

Claims 35-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification provides adequate written description for SEQ ID NO:2, but not angiogenically active variants or fragments thereof. The instant claims are directed to polypeptides set forth in SEQ ID NO:2 or variants or derivatives thereof. There is insufficient descriptive support for "angiogenically active fragments or variants of FGF-2 (SEQ ID NO:2) ". The claimed invention is drawn to a method for treating a human patient for congestive heart. The instant method requires the use of undisclosed angiogenically active

fragments and variants of FGF-2 (SEQ ID NO:2). The specification does not demonstrate possession of the instant process steps which require the use of the undisclosed compounds. Because the genus is variant, SEQ ID NO:2 alone is insufficient to describe the genes.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of SEQ ID NO:2, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptide and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO:2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
November 22, 2003

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